GastroPlus® Simulations to Monolix™ for Trial Design

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Please note: this presentation, including questions from the audience, is being recorded and may be made available.

Objectives

- Validate a mechanistic in vitro-in vivo correlation
- Predict the clinical PK of formulation variants
- Perform Virtual Bioequivalence
- Design a Bioequivalence clinical trial

Workflow

In vitro release and corresponding PK profiles

Validation of IVIVC

Simulation of clinical PK for formulation variants

PBBM-PBPK based VBE

Monolix ready populations

Reference model

Formulation covariates

Bioequivalence trials simulations

SimulationsPlus
MIDD+
Model Informed Drug Development + 2023

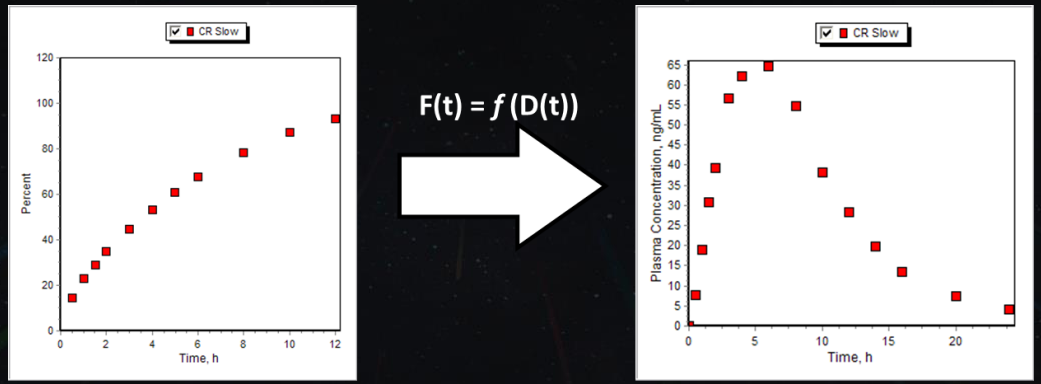
SimulationsPlus

IVIVC

Working definition:

"A predictive mathematical treatment describing the relationship between an *in vitro* property of a dosage form (e.g., the rate or extent of drug release) and a relevant *in vivo* response (e.g., plasma concentration-time data)"

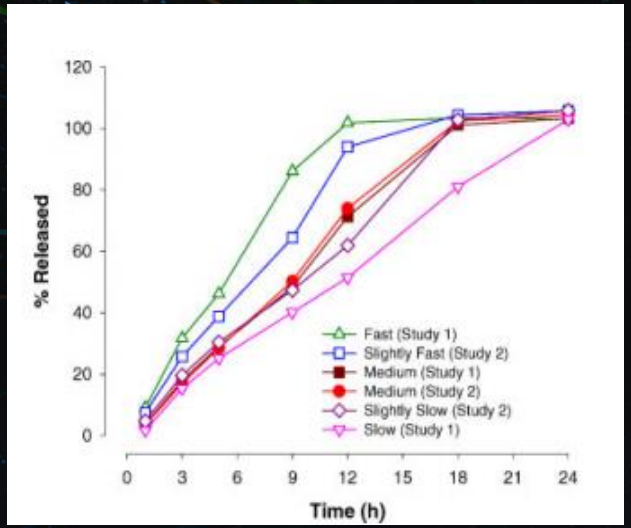
FDA Guidance for Industry Extended Release Solid Oral Dosage Forms: Development, Evaluation, and Application of *In Vitro/In Vivo* Correlations (1997)

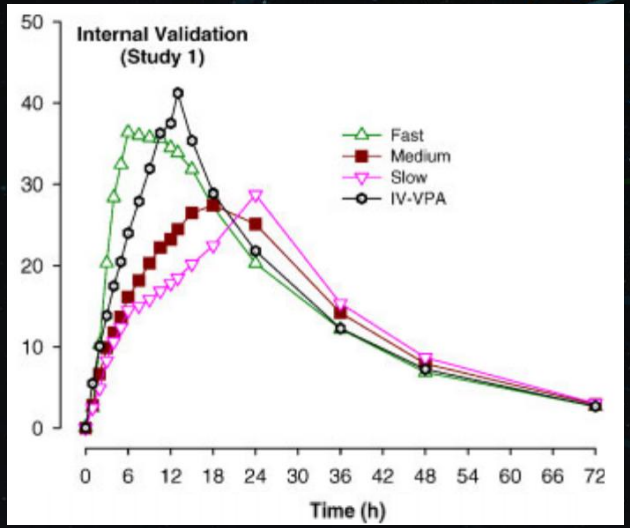


In vitro

In vivo

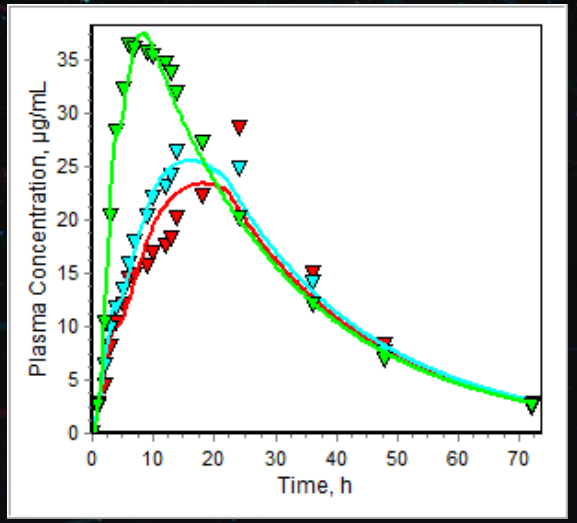
IVIVC for Valproate



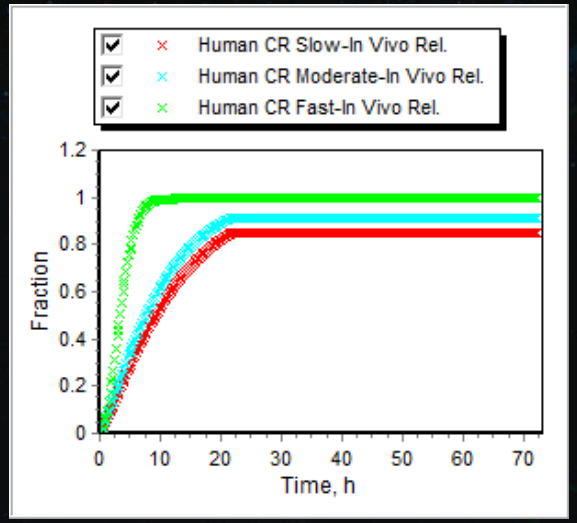


Dutta, et al, J PHARM SCI, 2005, 94(9), 1949-1956

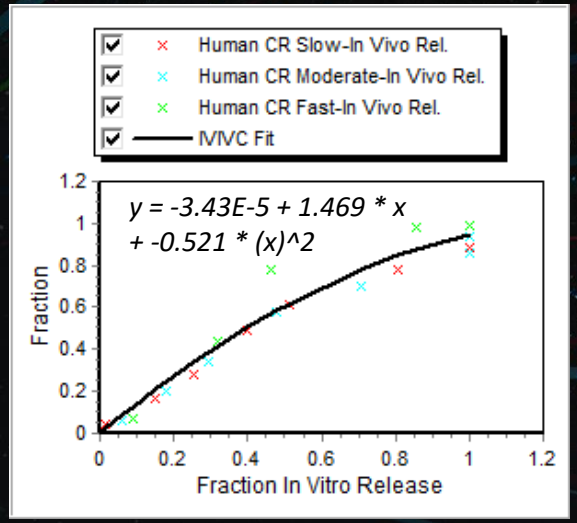
IVIVC development



Deconvolution

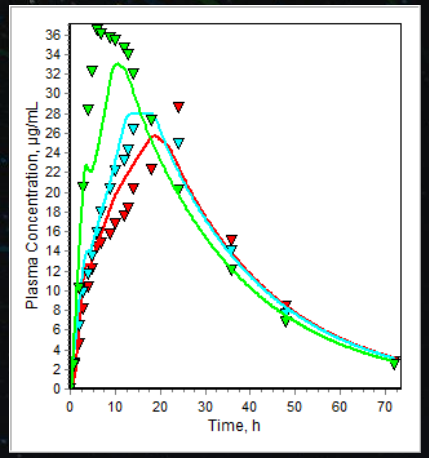


Correlation



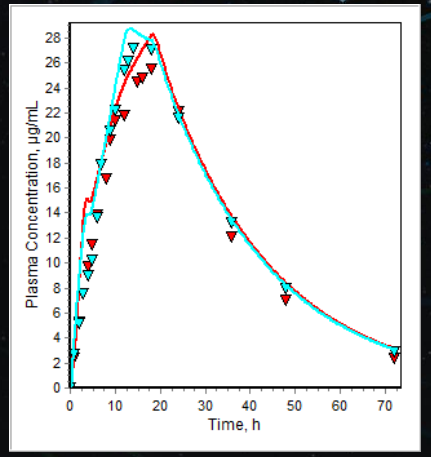
IVIVC Validation

INTERNAL



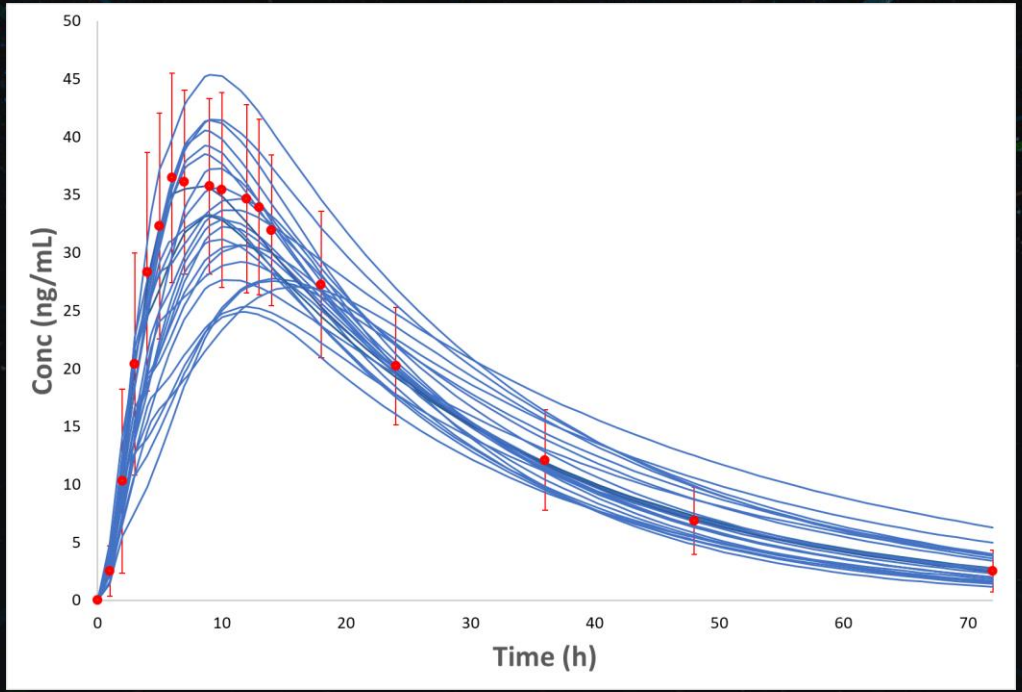
Drug Record	Cmax % Pred. Error	AUCt % Pred. Error
Human CR Slow	10.31	1.383
Human CR Moderate	-2.295	-1.57
Human CR Fast	9.481	5.202
Mean Absolute Percent Prediction Error	7.362	2.718

EXTERNAL



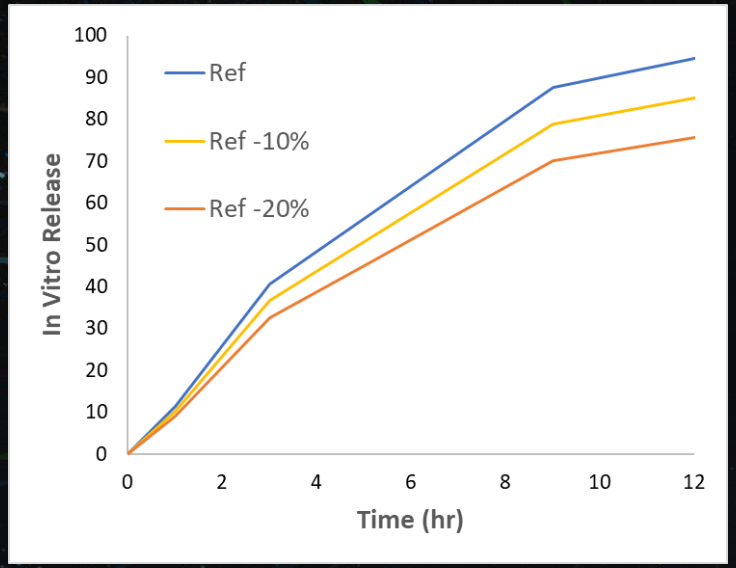
Drug Record	Cmax % Pred. Error	AUCt % Pred. Error
Mean Absolute Percent Prediction Error	8.23	9.089

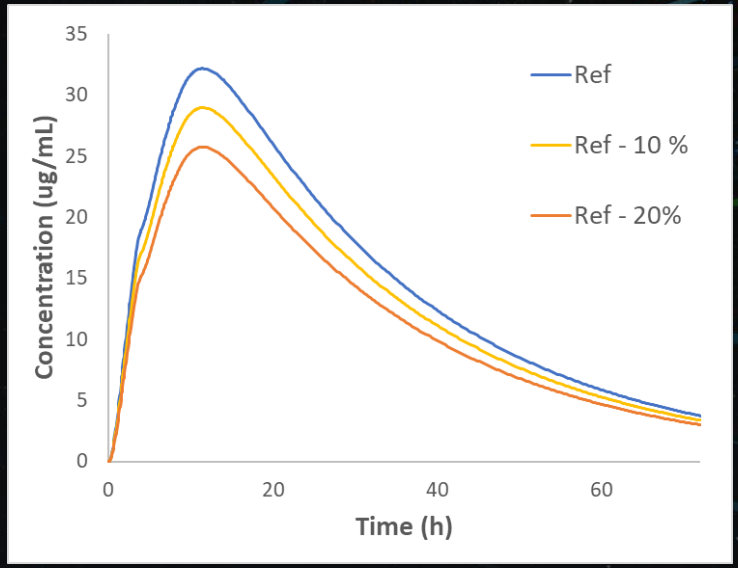
Intersubject variability



25 individual simulations for a virtual population representative of the clinical trial demographic

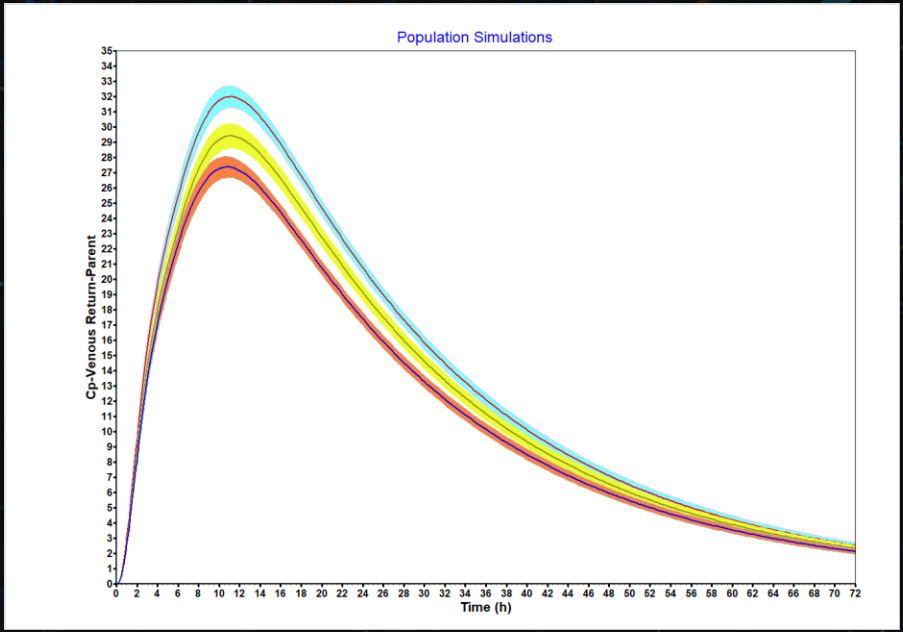
Formulation Variants





IVIVC-based predictions

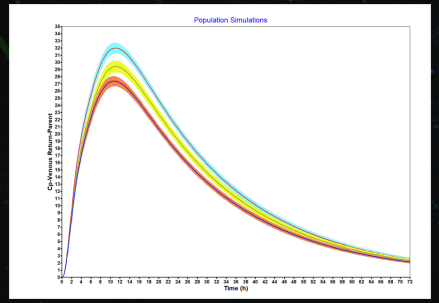
Virtual Bioequivalence

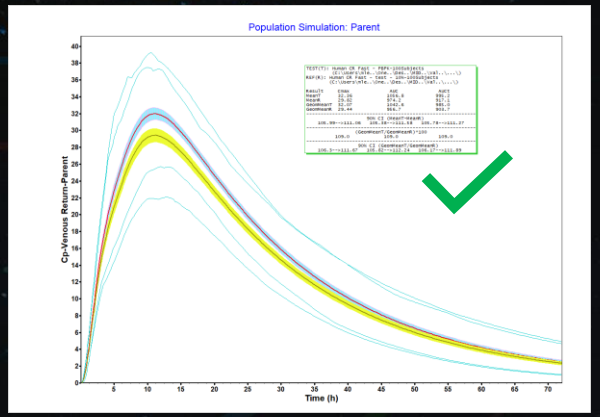


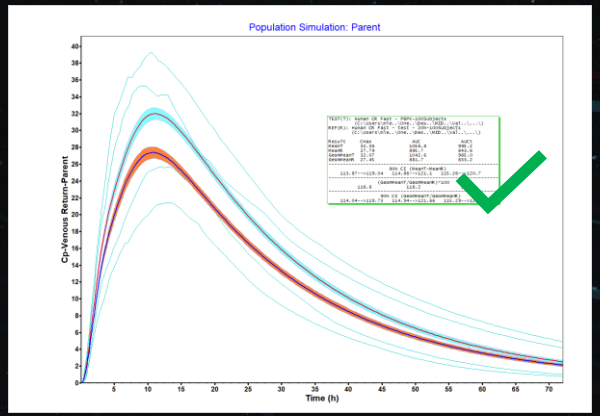
Virtual population of 100 individuals receiving the three formulation variants (with intrasubject variability)

- Ref → Ref -10 %
- Ref → Ref – 20 %

Virtual Bioequivalence







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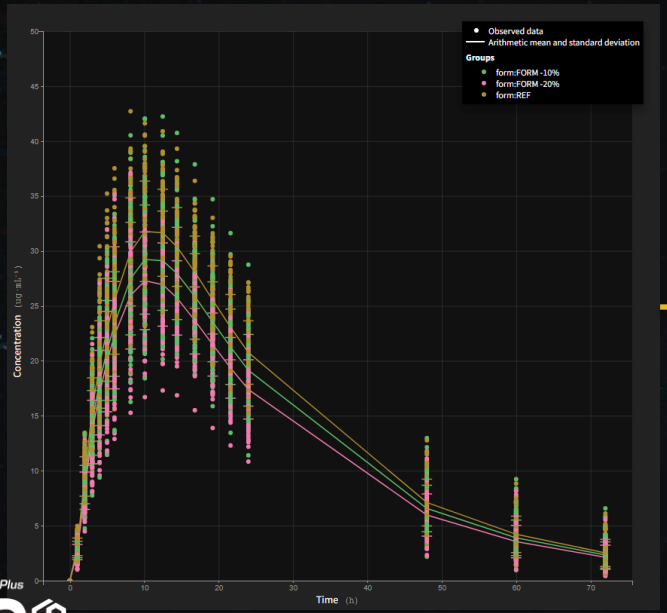
SimulationsPlus

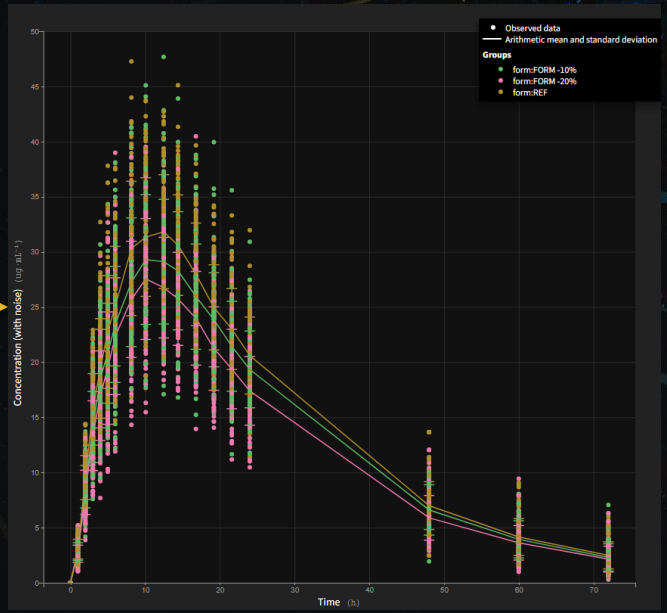
Toward clinical trial

- Add measurement noise to have a more representative data set
- Develop a population model to be able to easily simulate any clinical trial
- Simulate any clinical trial configuration (varying the number of subjects, varying the formulation, varying the blood sample times, …) and see the predicted power of this trial.

Adding measurement noise

- Prediction coming from GastroPlus® are too dense and too “clean”, a 10% proportional noise was added

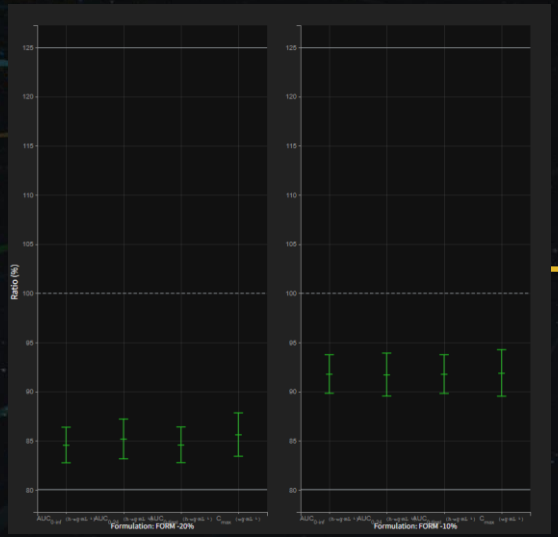




Adding measurement noise

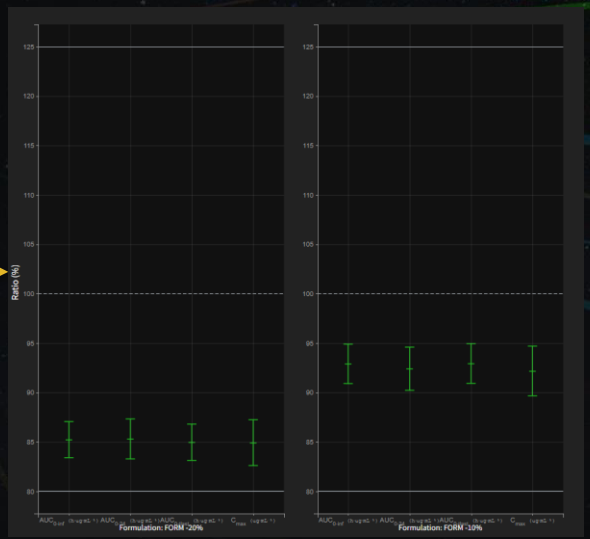
- Increase variability of the measurement
- No impact of mean PK metrics, nor on bioequivalence results

Bioequivalence results with original dataset



No impact on bioequivalence results

Bioequivalence results with "noisy" dataset



PopPK modeling

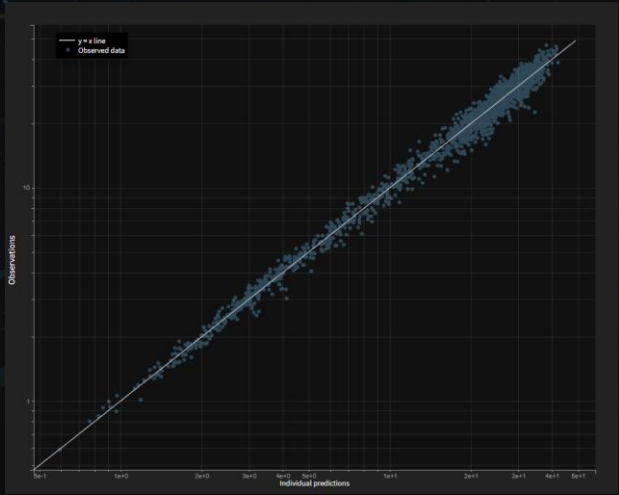
Using Monolix for popPK modeling, starting on the reference formulation

Population modeling of PK double absorption model
=> Already in Monolix model library

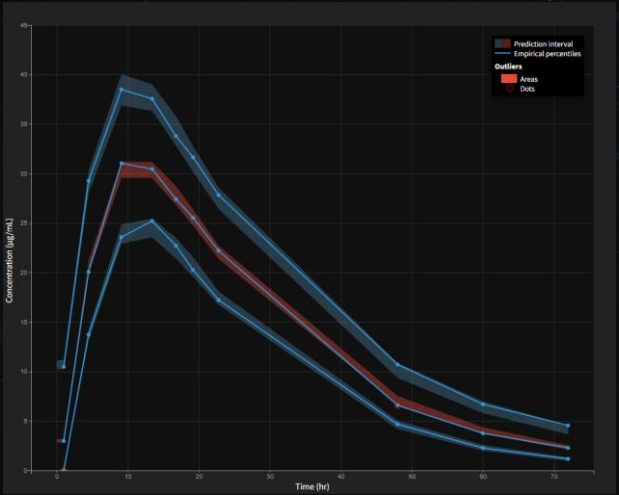
PopPK modeling

Resulting popPK model has a double extravascular absorption composed of a first order absorption with a lag-time and a simultaneous zero-order absorption with a lag-time longer than the first one

Observation vs prediction



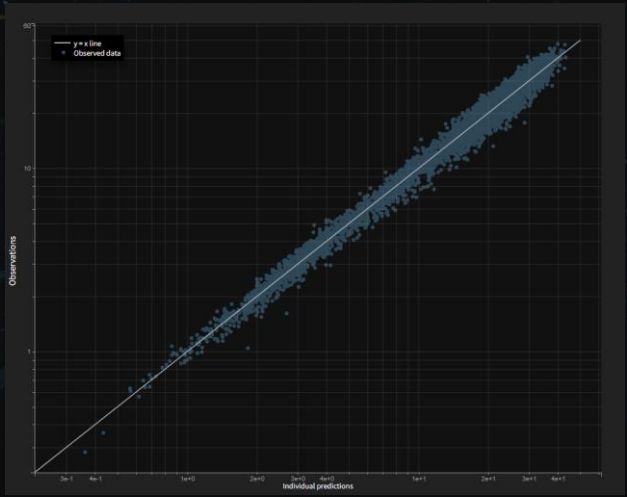
Virtual predictive check



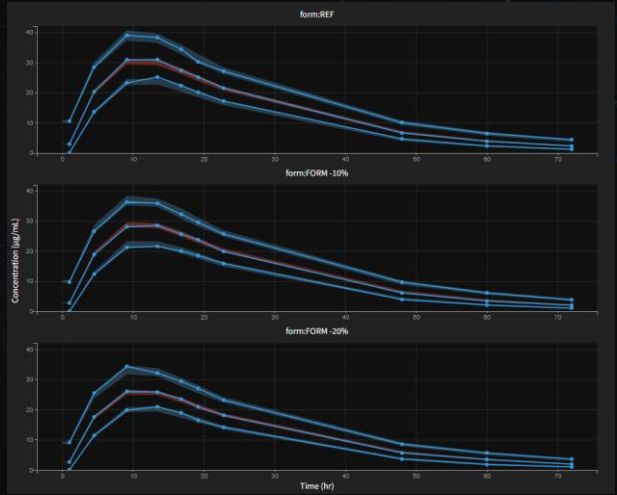
Full PopPK modeling

- Inclusion of the formulation as covariate and a bioavailability parameter varying with the formulation (as well as other absorption related parameters)

Observation vs prediction



Virtual predictive check



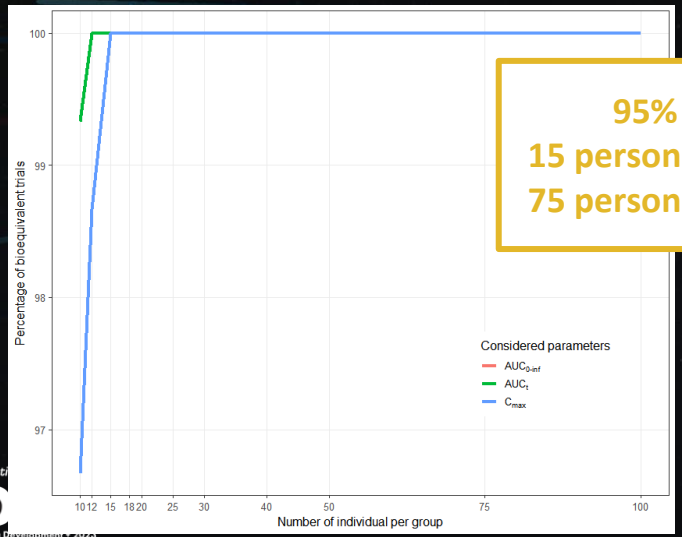
Using this population model to answer questions

- Use this model to perform simulations to answer operational questions such as
  - How many individuals should I enroll to ensure that my trial shows bioequivalence?
  - How many concentration measurements should I have to ensure bioequivalence?
  - What would the impact of a formulation changing the fraction between the two absorptions?
- In all cases, simulations in Simulx exported in PKanalix for bioequivalence calculation

How many individuals should I enroll to ensure that my trial shows bioequivalence?

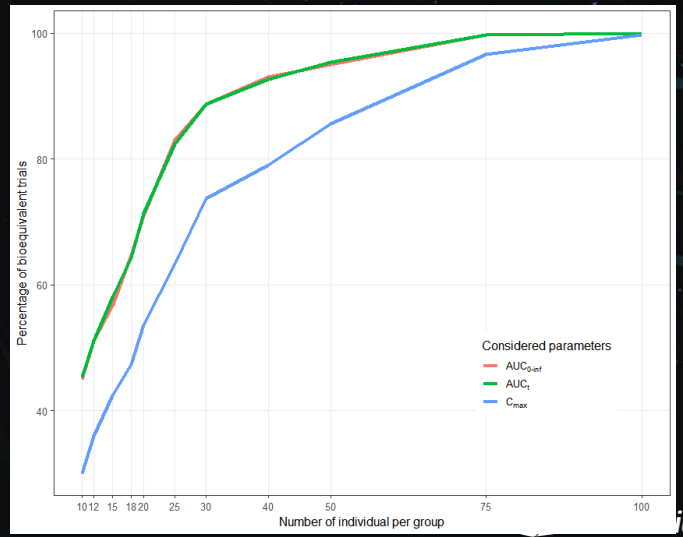
- Simulate a cross over trial with N individuals per group,
- Compute the bioequivalence on this trial
- Replicate that to compute the power of the trial

Form -10%



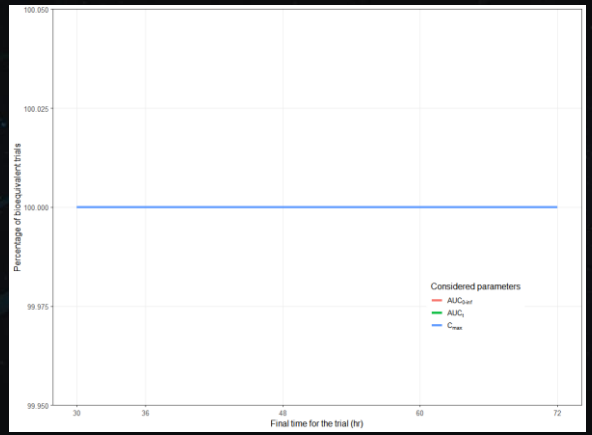
95% of success:
15 persons for FORM -10%
75 persons for FORM -20%

Form -20%



How many concentration measurements should I have to ensure bioequivalence?

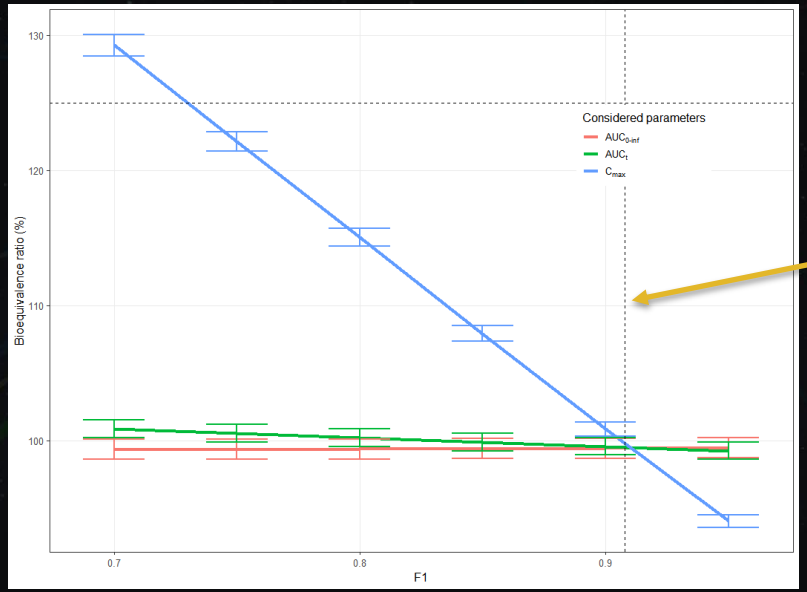
- Measurements at times 0, 1, 2, 4, 6, 8, 10, 12, 15, 18, 21, 24, 30, 36, 48, 60, 72. Simulate a cross over trial with 20 individuals per group, and different (remove 72, remove 60 and 72, …)
- Compute the bioequivalence on this trial
- Replicate that to compute the power of the trial



No impact of the final time on the bioequivalence

What would the impact of a formulation changing the fraction between the two absorption?

- Simulate a cross over trial with 500 individuals per group, change parameter F1 from its estimated value
- Compute the bioequivalence on this trial



Conclusion

- We were able to validate a mechanistic in vitro-in vivo correlation and predict the clinical PK of formulation variants
- We were able to use these data to develop a population model taking he formulation into account
- We used this model to perform concrete simulation to design any Bioequivalence clinical trial
- All of that using the interoperable solutions from Simulations Plus

SimulationsPlus

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Q&A

Questions & Answers